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Summary:

Background: The impact of compliance to clinical practice guidelines (CPG) on outcomes and/or costs of care has not been completely clarified.

Objective: To estimate relationships between medical expenditures and compliance to CPG for initial sarcoma treatment.

Research design: Selected cohorts of patients diagnosed with sarcoma in 2005 and 2006, and treated at the University hospital and/or the cancer centre of the Rhône-Alpes region, France (n=90). Main outcome measurements were: patient characteristics, compliance with CPG, health outcomes, and costs. Data were mainly extracted from patient records. The logarithm of treatment costs was modelled using linear and Tobit regressions.

Results: Rates of compliance with CPG were 86%, 66%, 88%, 89%, and 95% for initial diagnosis, primary surgical excision, wide surgical excision, chemotherapy, and radiotherapy, respectively. Total average costs reached €24,439, with €1,784, €11,225, €10,360, and €1,016 for diagnosis, surgery (primary and wide surgical excisions), chemotherapy, and radiotherapy, respectively. Compliance of diagnosis with CPG decreased the cost of diagnosis, whereas compliance of primary surgical excision increased the cost of chemotherapy. Compliance of chemotherapy with CPG decreased the cost of radiotherapy.

Conclusion: Since chemotherapy is one of the major cost drivers, these results support that compliance with guidelines increases medical care expenditures in short term.

Key Words: Oncology, Sarcoma, Cost, Clinical guidelines, Efficacy, Medical Practices

JEL Code: I18 – Government Policy; Regulation; Public Health

Introduction

Variations in medical practices have been the subject of extensive research [O' Connor et *al*. 1999; Akhtar et *al*. 2003; Jagsi et *al*. 2006; Neils et *al*. 2007]. In addition to medical reasons, these variations are generally explained by the organization of care, the level of supply of care and the dissemination of scientific knowledge. In order to reduce inappropriate medical practices, numerous Clinical Practice Guidelines (CPG) have been developed in recent decades [O' Connor et *al*. 2005]. CPG implementation has become a priority of healthcare policies and has hence received considerable research attention [Kaegi et *al*. 1991; Audet et *al*. 1991]. Compliance to CPG has been also widely studied even for rare cancers [Chassin et *al*. 1986; Ray Coquard et *al*. 1997; Ray Coquard et *al*. 2005]. A retrospective study analyzing the medical records of patients with sarcoma in two referent institutions of the Rhone-Alpes region, France (University hospital of Lyon and Cancer Center Léon Bérard) had shown that initial clinical management between 1999 and 2001 had been consistent with the CPG in only 32% of cases [Ray Coquard et *al*. 2004]. Because of this low percentage and the rarity of the tumour, a second study was initiated in 2005 to analyse the evolution of compliance over time. As the impact of compliance to CPG on health outcomes and costs of care has received less research attention [Fritz et al., 2007], the study initiated in 2005 also estimates the links (i) between compliance with CPG and costs of care in the short term; (ii) between compliance with CPG, health outcomes, and costs of care in the long term (80% of relapses occur during the first three years). The aim of this paper is to present the short-run economic analyses performed for comparisons in each referent institution, and to assess whether the idea that compliance with CPG generally increases medical care expenditures is also valid for rare tumours. In fact, this appears particularly

uncertain for sarcoma due to the clinical specificities (numerous histological subtypes, complexity of diagnosis, requirement for multidisciplinary medical decisions, etc.). In this disease, for instance, compliance of diagnosis with CPG is expected to decrease the cost of surgery.

Methods

Inclusion criteria

All patient aged 15 years and older, with an initial diagnosis of sarcoma made between March 2005 and February 2006, and treated at the University Hospital of Lyon and/or at the Cancer Centre of the Rhône-Alpes region, France, were eligible for the study.

Exclusion criteria

Patient treated for a non sarcoma tumour, relapsing patients (no CPG available), patients aged less than 15 years, those treated outside the University Hospital of Lyon and/or the Cancer Centre of the Rhône-Alpes region, or treated before March 2005 or after February 2006 were excluded from the study.

Clinical practice guidelines

The Clinical Practice Guidelines (CPG) is a nationwide project of the Fédération Nationale des Centres de Lutte contre le Cancer (French Federation of Comprehensive Cancer Centers, FNCLCC). The CPG for the clinical management of sarcoma used in this study were based on Standards-Options and Recommendations (SOR) published in 1995 and updated in 2004 [FNCLCC 1995].

Main outcome measurement

Patient characteristics: In addition to patient age and sex, we also distinguished low, intermediate and high-grade tumours. The size and depth of the tumour were noted, as well as severe concomitant or past diseases. Three tumour localizations were considered (bone, soft tissue, and viscera), as well as three tumour sites (head and/or neck, limb, and trunk).

Compliance with CPG: Each medical procedure was individually assessed for conformity with CPG. The CPG for each sequence of treatment are detailed in appendix 1. Only medical decisions covered by the CPG were taken into consideration for assessing compliance. The number of medical decisions judged to be based on multidisciplinary medical decision was also taken into account [Ray-Coquard 1997; Ray-Coquard 2002; Castel et al. 2004; Ray-Coquard 2005]. Overall treatment was considered to be compliant when all treatment sequences were compliant (i.e. diagnosis, primary and wide surgical excisions, chemotherapy, and radiotherapy).

Health outcomes: Indicators of efficacy at completion of initial treatment and at one year were: complete remission, partial remission, stable disease, progressive disease and death.

Cost evaluation: Costs were assessed for each patient and for each sequence of care. Costs were calculated from the hospital's point of view, based on a micro costing approach [Drummond et *al*. 2005]. The time horizon ranged from diagnosis (including

initial biopsy) to end of initial treatment (excluding follow-up period). Thus, for each sequence of care and for each patient, the type and quantities of imaging, blood transfusion and surgical procedures, as well as the type and length of hospitalisations were recorded. The types of initial biopsies, chemotherapy drugs, and radiation treatments were also identified. The resources used were then multiplied by unit costs or prices, respectively. Estimates were based on 2006 prices and costs.

Data source

Data related to the characteristics of the patients and the resources used were extracted from patient records in the two hospitals. Compliance with CPG was analyzed and double-checked by two authors (medical oncologists). Prices were taken from the Classification Commune des Actes Médicaux (CCAM) and the Bulletin Officiel de la République Française, whereas costs were calculated by the accounting departments of the University hospital and the Cancer Centre.

Statistical and econometric analysis

Descriptive statistics were used to analyze patient characteristics, costs of treatment, and health outcomes. Multiple regression analyses were performed to examine the relationship between the cost of each treatment sequence and a range of explanatory variables, including compliance. The medical variables considered relevant for each sequence of initial treatment were retained. Complementary regressions -available upon request from the authors- showed that most of these variables were not correlated to variations of compliance. Consequently, there was no problem of multicollinearity between costs and compliance. The technique for regression analysis depended on the

nature of the data. More precisely, the logarithm of treatment costs at each stage was estimated using standard linear models with Ordinary Least Squares (OLS) when the cost variable was continuous, and Tobit regression when the cost variable was censored so that the data contained a large proportion of zero values. OLS regression is calculated as follows:

$$y_i = X_i\beta + u_i \qquad (1)$$

where y_i is the dependent variable, i.e. the log of the total cost, X_i is a vector of independent variables, β is a vector of unknown coefficients and u_i is an independently distributed error term assumed to be normal with zero mean and constant variance σ^2.

The stochastic model underlying Tobit may be expressed by the following relationship:

$$y_i = \begin{cases} X_i\beta + u_i & if \quad X_i\beta + u_i > 0 \\ 0 & if \quad X_i\beta + u_i \le 0, \end{cases} \qquad (2)$$

where u_i follows a normal distribution with zero mean and constant variance σ^2. The same regressions were also done at a more disaggregated level, i.e. distinguishing the different expenditures associated to each sequence. Results are not reported here but are available on request from authors.

As the percentage of radiation therapy was very low, which was in contradiction with CPG, regression analysis with radiation therapy was not possible. For all analyses, statistical significance was set at 5% and 10%. Calculations were performed using Stata 10.0 software.

Results

Descriptive statistics

Characteristics of patients: Main characteristics of patients are described in table 1. The average age of patients at the date of histological examination (n=84) was 54 years, ranging from 17 to 86 years. More precisely, 32 patients (38%) were less than 50 years old; 33 (39%) were between 50 and 69 years old, 19 (23%) were 70 years old and over. Most (57%) patients were female. A majority of high-grade tumours (36%) were observed. Only 19 tumours (23%) were low-grade. Sarcomas were mainly located in soft tissues (63%) and the most frequent tumour site was the trunk (54%). Most tumours were deep-seated (65%) with an average size of 97mm, ranging from 16 to 320mm. Tumour size was lower than or equal to 50 mm in 33 % of the patients (n=26) and 100 mm in 68 % (n=53). Moreover, 23 patients (27%) had other severe concomitant or past diseases: 20 previous cancers and 3 severe concomitant diseases such as VIH (n=2) and haemophilia (n=1). Twelve patients (14%) had metastases at diagnosis of sarcoma. Surgery was contraindicated for 6 patients (7%) in whom the procedure would be too mutilating.

Description of patient management: The average time interval between the date of first symptoms and the date of diagnosis was 156 days (n=69), ranging from 8 to 1821 days. A majority of patients (54%, n=37) were diagnosed with sarcoma between 1 and 3 months after the first symptoms, and 23% (n=16) received appropriate treatment more than three months after the first symptoms.

Initial sarcoma treatments were as follows:

- Thirty patients (36%) were treated with surgery alone. Most of them had low-grade tumours (37%), mainly, located in the soft tissues (67%), and the trunk was the most frequent tumour site (67%).

- Eight patients (10%) received only chemotherapy. Most of them had intermediate-grade tumours (38%), mainly located in the soft tissues (63%), and the trunk was the most frequent tumour site (63%).
- One patient (1%) with an unknown grade tumour of the soft tissues arising in limb received only radiation therapy.
- Twelve patients (14%) had both surgery and chemotherapy. Most of them had high-grade tumours (58%) located equally in the bones, the soft tissues, and the viscera. Trunk was the most frequent tumour site (63%).
- Twelve patients (14%) had both surgery and radiation therapy. Most of them had high-grade tumours (58%), mainly located in the soft tissues (100%), and limb was the most frequent tumour site (58%).
- Five patients (6%) received both chemotherapy and radiation therapy There was a majority of unknown grade tumours (40%), mainly located in the soft tissues (60%), and limb was the most frequent tumour site (60%).
- Fifteen patients (18%) received all three treatments. Most had high-grade tumours (47%), mainly located in the soft tissues (53%), and trunk was the most frequent tumour site (40%).
- Finally, 1 patient (1%) did not have any treatment because of age.

Diagnosis: All patients underwent complete diagnostic evaluation (imaging, consultation with a physician, biopsies, etc.). Fourteen patients (17%) had cytologic examination, 12 (15%) had a micro-biopsy, 25 (31%) had a surgical biopsy, 27 (34%) had both cytologic examination and a micro-biopsy, 1 patient (1%) had both a micro-

biopsy and a surgical biopsy, and 2 patients (2%) underwent all three diagnostic procedures.

Surgery: Primary surgical resection (excluding biopsies) was performed in 68 patients (81%): 34 (50%) R0, 25 (37%) R1, and 9 (13%) R2 surgical resections. Eight patients (12%) had wide, R0 surgical resections. One patient (1%) underwent surgical resection of a metastasis during initial treatment of sarcoma. The surgeons performing these procedures (primary and wide surgical excisions) were specialized in digestive and/or visceral surgery (42%), in otolaryngology or cardiac, plastic, and neural surgery (26%), in cancer surgery (7%), or in orthopaedic and trauma surgery (5%).

Chemotherapy: Forty patients (48%) received chemotherapy in the neoadjuvant (23 patients, 57%), adjuvant (11 patients, 28%) or palliative (6 patients, 15%) settings.

Radiation therapy: Radiation therapy was performed after surgery in 27 patients (82%), before surgery in 3 patients (9%), and with palliative intent in 3 patients (9%).

Lastly, respectively 6 (7%), 14 (17%), and 4 patients (5%) received surgery, chemotherapy, and radiation therapy after initial treatment.

Compliance with clinical practice guidelines:

Initial treatment was compliant with CPG in 41 (53%) cases. More precisely, compliance rates were 86% at diagnosis, 66% at primary surgery, 89% at chemotherapy, and 95% at radiation therapy. Results are detailed in table 2.

Health outcomes: Main health outcomes at the end of initial treatment and survival rates after one year are detailed in table 3. Complete remission was achieved at the end of initial treatment in 71% of the patients. At one year, only fifty-one patients (61%) were

still in complete remission, and six of those who were in complete remission at the end of initial treatment had died. Amongst the fourteen deaths reported at one year, 13 were directly attributable to sarcoma.

Costs of initial treatment: Average costs per treatment sequence are reported in table 4. The average cost of initial sarcoma treatment reached €24,439 (n=79), ranging from €2,040 to €72,780. The procedures were ranked based on all observed costs, even when the cost of a sequence was set at zero. Surgery (primary and wide surgical excisions), with an average cost of €11,225, represented 45% of the average total cost. Next came chemotherapy (€10,360) with 43% of the average total cost, followed by diagnosis (€1,784) with 7%, and radiation therapy (€1,016) with 5%. However, the average cost of chemotherapy for the 40 patients who did receive chemotherapy (three missing data due to unknown prices for drugs used within clinical trials) reached €22,679. Surgical treatment reached €13,535 for the 68 patients who actually had surgery, and the cost of radiotherapy was €2,554 for the 33 patients who actually had radiation therapy.

Econometric analyses of treatment costs

Correlation between costs and medical variables: As shown in table 5, the smaller the tumour, the higher the average total cost of diagnosis (p=0.031). Regression analyses at a more disaggregated level revealed that the size of the tumour negatively impacted the average cost of hospitalization for diagnosis (p=0.015), but did not significantly influence the other types of expenditures for this sequence, e.g. expenditures related to biopsy or imaging. The depth of the tumour did not significantly influence the average

total cost of diagnosis, even though a deep tumour increased the average cost of diagnostic imaging ($p=0.001$).

The average total cost of surgery (primary and wide surgical excisions) depended on the size and location of the tumour, the presence of metastases at diagnosis, and the administration of neoadjuvant treatment: (i) The larger the size of the tumour, the higher the average cost ($p=0.093$). (ii) Average total costs were also higher for tumours arising in bone compared to soft tissues ($p=0.015$). (iii) However, metastases at diagnosis, as well as neoadjuvant treatment(s), decreased the average total cost of surgery ($p\leq0.001$). At the disaggregated level, all results regarding the average cost of hospitalization for surgery were confirmed. Moreover, the average cost of imaging for surgery was higher when the site of the tumour was limb compared to head and neck ($p=0.061$). The mean cost of transfusions for surgery increased with the size and the depth of the tumour, as well as for intermediate and high grades compared to low grade.

The average total cost of chemotherapy increased with the occurrence of other diseases ($p=0.088$), for intermediate or high-grade tumours ($p<0.001$), and with neoadjuvant chemotherapy ($p<0.001$). This cost was also higher for patients with metastases at diagnosis ($p=0.002$). In addition, the younger the patient, the higher the average total cost of chemotherapy ($p=0.069$). Results were confirmed at the disaggregated level for. the average costs of chemotherapy drugs, transfusions, and imaging, but not for the occurrence of "other diseases" which had no impact on the average costs of imaging. However, the tumour site seemed to be an additional determinant influencing the average cost of chemotherapy drugs: this cost was smaller for tumours arising in the head and/or neck ($p=0.076$) and in trunk ($p=0.096$) compared to limb. Average costs of hospitalization for chemotherapy were higher for intermediate and high-grade tumours

(p<0.001), for tumours located in bone compared to soft tissues (p=0.067), for younger patients (p=0.071) and for patients receiving neoadjuvant chemotherapy (p<0.001). Average costs of transfusions for chemotherapy increased only for intermediate and high-grade tumours (p=0.008) and for younger patients (p=0.006).

The average total cost of radiation therapy increased for deep tumours (p=0.004) and for intermediate and high-grade tumours (p=0.013). The mean total cost of radiation therapy also increased for soft-tissue compared to visceral tumours (p=0.010), and for younger patients (p=0.014).

Correlation between costs and compliance to CPG: As shown in table 5, compliance of diagnosis with CPG decreased the average total cost of diagnosis (p=0.071). More precisely, procedures compliant with CPG reduced the average cost of diagnosis by approximately 47% as compared to non compliant ones. This impact of diagnosis compliance on the total cost of diagnosis had opposite effects on the different cost items associated with diagnosis: the average cost of hospitalization for diagnosis also decreased with compliance of diagnosis with CPG (p=0.064), whereas the average cost of diagnostic imaging and biopsy increased (p≤0.001). No impact on the costs of other sequences of initial sarcoma treatment (surgery, chemotherapy and radiation) was observed.

Compliance of primary surgical resection with CPG did not influence the total cost of surgery. However, it was associated with an increased average total cost of chemotherapy (p=0.033). We could evaluate this impact by calculating the expected value of the log cost (y_i) in the model using the following formula:

$$E(y_i) = X_i\beta\Phi(X_i\beta/\sigma) + \sigma\phi(X_i\beta/\sigma) \qquad (3)$$

where Φ is the cumulative normal distribution function and ϕ the standard normal density.

For example, the average total cost of chemotherapy for a 54-year-old patient receiving neoadjuvant treatment, without other severe diseases, was 16 times higher when primary surgical resection was compliant. There can be two reasons for this: i) compliance increased the number of patients who received chemotherapy; ii) compliance increased the cost of chemotherapy amongst patients who received chemotherapy. The Tobit regression model can be used to evaluate both components [McDonald and Moffitt 1980]:

- the probability of having a positive cost:

$$Prob\,(y_i > 0) = \Phi(X_i\beta/\sigma) \quad (4)$$

- the value of the cost if it is already above zero:

$$E(y_i | y_i > 0) = X_i\beta + \sigma[\phi(X_i\beta/\sigma)/\Phi(X_i\beta/\sigma)] \quad (5)$$

For a 54-year-old patient on neoadjuvant treatment, without other severe diseases, the probability of receiving chemotherapy was 79% if the primary surgical resection was compliant with CPG, and 45% otherwise. For patients undergoing chemotherapy, compliance of primary surgery to CPG multiplied the average cost of chemotherapy by 7.5.

At the disaggregated level, we noted that compliance of primary surgery with CPG increased the main cost items associated with chemotherapy: average cost of drugs (p=0.032), hospitalization (p=0.097), and imaging (p=0.028).

Compliance of chemotherapy with CPG did not influence the average cost of chemotherapy, whereas it decreased the average total cost of radiotherapy (p=0.031).

The cost reduction associated with compliance of chemotherapy was important: for a 54-year-old patient with a deep, high-grade tumour, the average total cost of radiation therapy was multiplied by 114 when chemotherapy was not compliant. Compliance of chemotherapy decreased the probability of having radiation therapy from 91% to 58%.

Discussion

Compliance with CPG seems to increase the costs of initial treatment

Considering that compliance of primary surgery (excluding biopsy) significantly increases the average total cost of chemotherapy (higher number of patients receiving a chemotherapy; higher cost of chemotherapy amongst patients receiving chemotherapy), and that compliance of chemotherapy increases the cost of hospitalisation for chemotherapy (average length of stay 24.8 versus 13.1 days with and without compliance, respectively) and the cost of chemotherapy drugs (3,770€ versus 2,474€ with and without compliance, respectively), compliance with CPG seems to increase medical expenditures for the initial treatment of sarcoma. As shown in the results, chemotherapy is the most expensive treatment sequence because of the cost of chemotherapy drugs, i.e. 27% more expensive than diagnosis, surgery and radiation therapy together. Our results, like other published studies [Ozminkowski et *al*. 2000], demonstrate that it may be cheaper in the short term to deviate from CPG. However, this should not encourage health providers to do so since better care, measured by compliance with CPG, could lead to better outcomes in the long term, in particular to fewer relapses.

Following patients longer than one year might help identify cost savings that eventually result from better care. However, the literature also suggests that compliance with CPG

decreases costs as, for example, for ischemic stroke management [Quaglini et *al*. 2004] or for patients with acute low back pain [Fritz et *al*. 2007]. The contradictory results reported in the literature regarding compliance with CPG and costs required distinguishing between the different treatment sequences. Our results confirm that compliance of diagnosis with CPG decreases the average total cost of diagnosis, and that compliance of chemotherapy with CPG decreases the average total cost of radiotherapy. Moreover, this study is clearly based on "standard CPG" developed by the medical profession and used predominantly by physicians with the intent to reduce clinical variations and to further enhance the quality of care. The role of the guidelines is now expanding and changing whereby more and more guidelines are aimed at the reduction of health care costs [Callens et *al*. 2007].

A recent study by J.E. Butrynski et al. based on a large US health insurance database from 2002 to 2006 shows an average monthly medical cost of soft tissue sarcoma of $3,168 [Butrynski et al. 2008]. In our study sample, a focus on the 53 patients treated for soft tissue sarcoma shows an average monthly cost of €3,046 for diagnosis, surgery, chemotherapy and radiation therapy (i.e. $3,601 at the January 2006 exchange rate of 1.18210 euro per US dollar). The cost of care for soft tissue sarcoma reaches $38,016 per year and per patient in the J.E. Butrynski study, versus $43,207 in our study. Surprisingly, the average total cost is higher in France than in the US. Independently of numerous biases which could explain these results, the major difference lies with the type of treatment received: in the J.E. Butrynski study, respectively 18%, 35%, and 28% of the patients received chemotherapy, surgery, and radiation therapy compared to 48%, 82%, and 39% in our study. Those differences could be a consequence of the application of "classic" versus "cost minimisation" guidelines.

Relevance of results from the clinical point of view

Metastases at diagnosis increase the average cost of treatment because the CPG advise the use of chemotherapy. On the other hand, neoadjuvant chemotherapy decreases the complexity of the surgical procedure, thus reducing the cost of surgery. Moreover, younger patients more frequently receive chemotherapy and radiotherapy, which increases medical expenditures. This result is in agreement with other studies, such as the one showing that older patients generally receive less aggressive anti cancer treatments [Battaglia et *al*., 2006]. As visceral tumours are seldom treated with radiation therapy, it appears relevant that average costs of radiation therapy for this localisation are lower than for soft tissues. Compared with the results of a medical study performed between 1999 and 2001 in the same two hospitals, compliance of primary surgery and radiation therapy with CPG increased by 14 points, whereas compliance of chemotherapy decreased by 5 points, following the publications of another analysis which did not recommend chemotherapy for soft tissue sarcomas [Earl et *al*. 1998]. As shown in the literature, the elaboration of a series of recommendations within the framework of a network significantly improved the compliance of practices, and this effect persisted over time [Mille et *al*. 2000; Ray Coquard et *al*. 2002].

Limitations of the study

(1) At one year after the end of initial treatment, the prognosis of sarcoma is generally good. This is the reason why this study did not analyse the relation between compliance with CPG and health outcomes. Hence our findings cannot, at this stage, support or

refute the idea that compliance with CPG improves patient outcome [Bahtsevani et *al*. 2004].

(2) Comparing hospitals that treat different patient populations, and increasing the number of inclusions might provide useful information. In fact, hospitals with fewer and weaker patients generally have lower compliance with CPG [Goldman et *al*. 2007]. Increasing the number of inclusions should also permit to include in the regression analysis the time between the date of first symptoms and the date of diagnosis, the distance between patients' home and hospital, the speciality of the surgeon, as well as the possibility for patients to receive second-line surgery, chemotherapy and/or radiation therapy.

(3) Costs related to the development of the guidelines (data collection, elaboration and agreement of CPG) and to their implementation (dissemination of the CPG) were not taken into account. Also, due to the high number of variables and the experimental design of the study, a non-societal perspective was adopted. However, both limitations are generally observed in the literature [Vale et *al*. 2007].

In conclusion, this study shows multiple correlations between compliance, medical variables and costs within and across the sequences (i.e. diagnosis, surgery, chemotherapy, and radiation therapy) of initial sarcoma treatment. These results warrant further analysis with more patients, more types of hospitals (e.g. non reference hospitals), and longer follow-up (80% of relapses occur during the first three years of management), especially because (i) compliance of the initial treatment of sarcoma with CPG seems to be more expensive in the short run but could reduce medical

expenditures in the long run; (ii) few studies have examined patient clinical outcomes and costs in relation to compliance with CPG [Fritz et *al*. 2007].

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References

Akhtar SR, Weaver J, Pierson DJ, Rubenfeld GD. Practice variation in respiratory therapy documentation during mechanical ventilation. *Chest* 2003; 124:2275-82.

Audet AM, Greenfield S, Field M. Medical practice guidelines: current activities and future directions. *Ann Intern Med*. 1990;113:709-14.

Bahtsevani C, Udén G, Willman A. Outcomes of evidence-based clinical practice guidelines: a systematic review. *Int J Technol Assess Health Care* 2004; 20:427-33.

Battaglia TA, Ash A, Prout MN, Freund KM. Cancer prevention trials and primary care physicians: factors associated with recommending trial enrollment. *Cancer Detect Prev*. 2006;30(1):34-7.

Butrynski JE, Duh MS, Fournier A, Moyneur E, Dial E, Neary MP, Demetri GD. Soft tissue sarcoma (STS): Challenges in identification, treatment patterns, and costs of disease management in the U.S. *J. Clin. Oncol*. 2008; 20 suppl; abstract 10573.

Callens S, Volbragt I, Nys H. Legal thoughts on the implications of cost-reducing guidelines for the quality of health care. *Health Policy* 2007;80:422-31.

Castel P, Blay JY, Meeus P, Sunyach MP, Ranchère-Vince D, Thiesse P et al. Organization and impact of the multidisciplinary committee in oncology. *Bull Cancer* 2004; 91:799-804.

Chassin MR, Brook RH, Park RE, Keesey J, Fink A, Kosecoff J et al. Variations in the use of medical and surgical services by the Medicare population. *N.Engl.J Med.* 1986;314:285-90

Drummond MF**,** Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes (Third edition)*: Oxford University Press; 2005.

Earl HM, Connolly S, Latoufis C, Eagle K, Ash CM, Fowler C et al. Long-term neurotoxicity of chemotherapy in adolescents and young adults treated for bone and soft tissue sarcomas. *Sarcoma* 1998;2:97-105.

FNCLCC. Standards, Options et Recommandations 1995 pour la prise en charge des patients adultes atteints de sarcome des tissus mous, de sarcome utérin ou de tumeur stromale gastro-intestinale. Site Internet: http://www.fnclcc.fr/sor.htm.

Fritz JM, Cleland JA, Brennan GP. Does adherence to the guideline recommendation for active treatments improve the quality of care for patients with acute low back pain delivered by physical therapists? *Med Care* 2007; 45:973-80.

Goldman LE, Vittinghoff E, Dudley RA. Quality of care in hospitals with a high percent of Medicaid patients. *Med Care* 2007;45:579-83.

Jagsi R, Makris A, Goldberg S, Taghian A. Intra-European differences in the radiotherapeutic management of breast cancer: a survey study. *Clin Oncol*. 2006; 18:369-75.

Kaegi L. Policy, management, and clinical practice implications get priority attention of health services researchers. *Qual Rev Bull*. 1991;17:297-304.

McDonald J. and Moffitt R. The Uses of Tobit Analysis. *The Review of Economics and Statistics* 1980; 62(2):318-321.

Mille D, Roy T, Carrere MO, Ray I, Ferdjaoui N, Späth HM et al. Economic impact of harmonizing medical practices: compliance with clinical practice guidelines in the follow-up of breast cancer in a French Comprehensive Cancer Center. *J Clin.Oncol*. 2000;18:1718-24

O'Connor GT, Quinton HB, Traven ND, Ramunno LD, Dodds TA, Marciniak TA et al., Wennberg JE. Geographic variation in the treatment of acute myocardial infarction: the Cooperative Cardiovascular Project. *JAMA*. 1999; 17:627-33.

O'Connor PJ. Adding value to evidence-based clinical guidelines. *JAMA*. 2005; 10:741-3.

Ozminkowski RJ, Wang S, Marder WD, Azzolini J Short-run associations between medical care expenditures and adherence to clinical practice guideline-based measures for diabetes *Value Health* 2000;3 Suppl 1:29-38.

Neils DM, Virgo KS, Longo WE, Ode K, Audisio RA, Shariff US, Papettas T et al. Geographic variation in follow-up after rectal cancer surgery. *Int J Oncol*. 2007; 30:735-42.

Quaglini S, Cavallini A, Gerzeli S, Micieli G; GLADIS Study Group (Guideline Application for the Decision making in Ischemic Stroke). Economic benefit from clinical practice guideline compliance in stroke patient management. *Health Policy* 2004;69:305-15.

Ray-Coquard I, Philip T, Lehmann M, Fervers B, Farsi F, Chauvin F. Impact of a clinical guidelines program for breast and colon cancer in a French cancer center. *JAMA* 1997;278:1591-5

Ray-Coquard I, Philip T, de Laroche G, Froger X, Suchaud JP, Voloch A et al. A controlled "before-after" study: impact of a clinical guidelines programme and regional cancer network organization on medical practice. *Br. J Cancer* 2002;86:313-21

Ray-Coquard I, Thiesse P, Ranchere-Vince D, Chauvin F, Bobin JY, Sunyach MP et al. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. *Ann Oncol.* 2004;15:307-15

Ray-Coquard I, Philip T, de Laroche G, Froger X, Suchaud JP, Voloch A et *al*. Persistence of medical change at implementation of clinical guidelines on medical practice: a controlled study in a cancer network. *J Clin Oncol*. 2005; 23:4414-23.

Vale L, Thomas R, MacLennan G, Grimshaw J. Systematic review of economic evaluations and cost analyses of guideline implementation strategies. *Eur J Health Econ*. 2007;8:111-21.

Table I

Characteristics of patients

Characteristics	Mean ±SD or number of patients (%)
Age (years) at histological evaluation	54.2 ± 18.7
Male / Female	36 (42.9%) / 48 (57.1%)
Tumour grade	
Low (grade I)	19 (22.6%)
Intermediate (grade II)	12 (14.3%)
High (grade III)	30 (35.7%)
Unknown / not applicable	11 (13.1%) / 12 (14.3%)
Tumour site	
Head / neck	11 (13.1%)
Limb	28 (33.3%)
Trunk	45 (53.6%)
Tumour localisation	
Bone	11 (13.1%)
Soft tissues	53 (63.1%)
Viscera	20 (23.8%)
Tumour size in mm[(1)]	97.0 ± 70.8
Tumour depth	
Superficial	6 (7.1%)
Deep	54 (64.3%)
Unknown / not applicable	23 (27.4%) / 1 (1.2%)

Other severe diseases (yes/no)	22 (26.2%) / 62 (73.8%)
Metastasis at diagnosis (yes/no)	12 (14.5%) / 71(85.5%)

(1) 6 missing data

Table 2

Compliance with Clinical Practice Guidelines

Compliance	Yes Number of observations (%)	No Number of observations(%)	Not applicable Number of observations
Diagnosis	72 (85.7%)	12 (14.3%)	-
Surgery			
- primary surgical resection-	55 (66.3%)	28 (33.7%)	-
- wide surgical resection-	29 (87.9%)	4 (12.1%)	50
- metastasis surgery-	11 (100%)	0 (0%)	72
Chemotherapy	74 (89.2%)	9 (10.8%)	-
Radiotherapy	74 (94.9%)	4 (5.1%)	-
Overall	41 (52.5%)	37 (47.5%)	-

Table 3

Health outcome

	At the end of initial treatment (number of observations)					
After one year	Complete remission	Partial remission	Stable disease	Progressive disease	Unknown	Total
Complete remission	51	1	0	0	0	52
Partial remission	0	2	0	0	0	2
Stable disease	0	1	4	0	0	5
Progressive disease	3	1	0	6	0	10
Death	6	0	2	6	0	14
Unknown	0	0	0	0	1	1
Total	60	5	6	12	1	84

Table 4

Average costs for each sequence (in €)

	Including zero values				Excluding zero values			
Sequence of treatment	n	Mean	(SD)	Range	n	Mean	SD	Range
Diagnosis	84	1,784	(2,090)	113- 11,360	84	1,784	(2,090)	113- 11,360
hospitalisation	84	1,410	(2,107)	0-11,019	46	2,575	(2,263)	918 - 11,019
imaging	84	228	(156)	0-718	82	233	(154)	21 -718
biopsy	84	82	(39)	0-178	81	86	(36)	53 - 178
consultation	84	64	(40)	0-90	62	90	-	90
Surgery	82	11,225	(9,792)	0-52,565	68	13,535	(9,174)	1,836 – 52,564
hospitalisation	82	10,997	(9,461)	0-47,750	68	13,261	(8,816)	1,836 - 47,750
transfusions	82	177	(607)	0-4,764	14	1,033	(1,157)	176 - 4,764
imaging	82	51	(99)	0-591	39	107	(120)	13 - 591
Chemotherapy	81	10,360	(15,332)	0-62,060	37	22,679	(15,535)	4,246 - 62,060
hospitalisation	81	8,156	(13,186)	0-55,600	35	18,874	(14,172)	2,195 - 55,600

chemotherapy drugs	81	1,767	(3,211)	0-15,904	37	3,867	(3,815)	175 - 15,904
transfusions	81	194	(553)	0-3,529	19	826	(897)	176 - 3,529
imaging	81	173	(264)	0-1,146	37	378	(273)	50 - 1,146
Radiotherapy	83	1,016	(2,547)	0-15,845	33	2,554	(3,546)	753 - 15,845
Total	79	24,439	(18,072)	2,040 -72,780	79	24,439	(18,072)	2,040 -72,780

Table 5

Regression analysis of the log of total costs for each sequence

Sequence	OLS Diagnosis		Tobit I Surgery		Tobit I Chemotherapy		Tobit I Radiation therapy	
	Coeff.	P>|t|	Coeff.	P>|t|	Coeff.	P>|t|	Coeff.	P>|t|
Age (continuous)	0.00253	0.729	-0.01635	0.469	-0.07938	0.069*	-0.13253	0.014**
Grade (1=grade II or III, 0=other)	0.12571	0.616	-0.07290	0.920	6.79740	0.000***	4.82491	0.013**
Site 1 (1=limb, 0=head/neck)	0.37335	0.419	-0.77919	0.558	-3.45416	0.142	0.50143	0.865
Site 2 (1=trunk, 0=head/neck)	0.43873	0.333	-1.00811	0.427	-3.39559	0.138	-0.09443	0.974
Localisation 1 (1=bone, 0=soft tissue)	0.15164	0.732	3.46461	0.015**	2.78043	0.198	0.67666	0.816
Localisation 2 (1=visceral,0=soft tissue)	0.10214	0.765	1.17450	0.233	1.69406	0.416	-8.67329	0.010**
Tumour size (continuous)	-0.00411	0.031**	0.00919	0.093*	-	-	0.01549	0.261
Tumour depth (1=deep, 0=other)	0.02854	0.914	1.15325	0.125	-	-	6.95255	0.004***
Other severe diseases (1=yes, 0=no)	0.01306	0.964	-0.52320	0.540	2.87816	0.088*	-2.25303	0.315

Metastasis at diagnosis (1=yes, 0=no)	-0.02786	0.944	-7.46264	0.000***	6.35471	0.002***	-1.74614	0.551
Neoadjuvant treatment [(1)]	-	-	-3.92367	0.001***	8.02959	0.000***	6.95418	0.116
Compliance of diagnosis (1=yes, 0=no)	-0.63056	0.071*	0.44044	0.659	-0.77074	0.763	3.43421	0.268
Compliance of primary surgery	-	-	-0.85275	0.321	4.54111	0.033**	-1.43287	0.495
Compliance of chemotherapy			-	-	2.63311	0.244	-6.33505	0.026**
Constant	7.26377	0.000***	9.03100	0.000***	-4.31161	0.278	3.01140	0.520
Number of observations	77		76		79		76	
Number of censored data	NA		12		43		47	
σ	NA		2.87858	0.267	4.96326	0.657	5.38555	0.806
Log-likelihood	NA		-170.803		-126.638		-107.980	

Note. [(1)] Neoadjuvant treatments are: Chemotherapy or radiation therapy when considering surgery regression; Neoadjuvant chemotherapy when considering chemotherapy regression; Neoadjuvant radiation therapy when considering radiation therapy regression.

*p<0.1; **p<0.05; ***p<0.01

Appendix 1

Main CPG criteria for each sequence of initial sarcoma treatment

Main Criteria for diagnosis: Clinical size and depth of the tumour mass must be recorded; Computed Tomography (CT) is required for abdominal localizations, or Magnetic Resonance Imaging (MRI) for limb localizations; Chest radiograph or CT scan is required to identify metastases; Initial biopsy (incisional or needle), preferably by the surgeon in charge of future surgical procedures, is required for bone and soft tissue sarcomas, with the exception of small tumours (<3 cm) for which excisional biopsy is considered appropriate.

Main Criteria for surgery: Whenever possible, primary surgery should involve a wide excision with 1–2 cm margins. For high-grade, large (>3 cm) or deep-seated tumours, surgery alone is acceptable only in case of amputation or compartimental resection with negative histological margins (R0). Wide excision alone, with no adjuvant treatment, is acceptable only for superficial, small (<3 cm) and low-grade lesions. Histologically positive margins (R1) or incomplete excision (R2) have to be considered inadequate, and should be followed by further appropriate treatment.

Main criteria for chemotherapy: For non-readily operable sarcomas, primary chemotherapy or radiation therapy can be an option. For readily operable sarcomas, neo-adjuvant chemotherapy should be performed only as part of a clinical research protocol. In the adjuvant setting, systemic chemotherapy should be performed only within the context of a prospective clinical trial. Adjuvant chemotherapy can be performed for patients with histologically positive margins after wide surgical excision.

Main criteria for radiation therapy: Association of wide surgical excision and adjuvant radiation therapy should be considered the standard treatment. The absence of adjuvant radiotherapy is

acceptable for superficial, small (<3 cm) and low-grade tumours, and for limb sarcomas when amputation is performed. For non-operable sarcomas, primary radiation therapy could be an option. The optimal treatment strategy involves a 50 Gy delivered dose with an additional boost of 10 Gy in case of microscopic residual tumour (R1), with a target volume encompassing the tumour bed and surgical scars, including draining orifices, with adapted security margins. Moreover, the interval from surgery to radiation therapy must not be longer than 8 weeks.